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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/762,376	07/20/2001	Chi-Huey Wong	TSRI 663.1	4021

7590 02/28/2005

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EXAMINER	
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/28/2005

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/762,376
Filing Date: July 20, 2001
Appellant(s): WONG ET AL.

Donald G. Lewis
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on 12-3-04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 7-9 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Steenbergen S.M. et al. "Functional analysis of the sialyltransferase complexes in E.coli K1 and K92" J. Bacteriol., Vol. 174, No. 4 (Feb 1992), pp 1099-1108.

Vann W.F. "A filter assay for polysialyltransferase" FEMS Microbiol. Lett., Vol. 128, (1995), pp.163-166.

Van Dijk et al. "Assay of nucleotide-sugar hydrolases" Anal.Biochem., Vol.117, No.2, (1981), pp. 346-353.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being obvious over Vann WF (FEMS Microbiology Lett., 1995, Vol. 128(2):163-166) or Steenbergen et al. (J.Bacteriol., 1992, Vol. 174(4):1099-1108) and Van Dijk et al. (Analytical Biochem., 1981, Vol. 117(2):346-353). This rejection is based on the public availability of a printed documents. Claims 7-9 of the instant application are drawn to a method of making polysialic acid product linked through α 2,8/2,9 linkage by contacting a sialic acid acceptor and a CMP-sialic acid donor with α 2,8/2,9-polysialyltransferase isolated from *E.coli* K92 under cell-free conditions for sequentially sialylating the sialic acid acceptor with CMP sialic acid donor followed by the step of removing the released CMP by treatment with alkaline phosphatase. It is well recognized in the art that the above strain of *E.coli* produces a unique polysialyltransferase which links sialic acid monomers through an alternate α 2,8/2,9 linkage. The above two references of Vann and Steenbergen et al. teach the partial purification, a cell-free composition comprising the

said enzyme and characterization of the polysialyltransferase from *E.coli* K92 and describes the method of making polysialic acid product by contacting a sialic acid acceptor and a CMP-sialic acid donor with said enzyme from *E.coli* K92 for sequentially sialylating the sialic acid acceptor with CMP sialic acid donor. However, both the above references use the step of paper filtration and chromatography to separate the product formed from released CMP as opposed to the step of removing the released CMP by treatment with alkaline phosphatase as claimed in the instant claims.

The reference of Van Dijk et al. teaches the use of alkaline phosphatase enzyme for removal of nucleotide phosphate and specifically from CMP nucleotide in a CMP-sialic hydrolase assay. Thus it appears that the use of phosphatase enzyme to remove the nucleotide sugars was well known in the art.

Therefore, combining the teachings of the above two references with that of Van Dijk et al., it would have been obvious to those skilled in the art, specifically those involved in developing an alternate method to the filtration method of making a polysialic acid product as described by Vann or Steenbergen et al., to collect the actual polysialic acid product formed and treat the reaction mixture with alkaline phosphatase to remove the CMP side product as taught by Van Dijk et al. One of ordinary skill in the art would be motivated to do so because, there would be no loss of product formed by treating the reaction mixture with alkaline phosphatase enzyme and the product formed can be collected, further purified and used for several practical applications. One of ordinary skill in the art would have a reasonable expectation of success since Vann and Steenbergen et al. already put in place a method of making the polysialic acid product and Van Dijk et al. suggest the use of alkaline phosphatase to remove the nucleotide sugar side from the main product formed. Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

(11) Response to Argument

In response to the above rejection, appellant traverses the rejection arguing that Steenbergen et al. discloses that *Escherichia coli K92* synthesizes a sialyl a2,9- a2,9 linked polymer and discloses an initial molecular description of K1 and K92 sialyltransferase and a partial purification of K92 sialyltransferase within a membrane bound fraction, and that Steenbergen discloses that K92 sialyltransferase has sialyltransferase activity, but does not disclose that K92 sialyltransferase has polysialyltransferase activity and that the reference discloses a suggestion, supported by genetic evidence only, that a single gene product in *Escherichia coli* K92 is capable of synthesizing a α2,8-2,9 polymer. Examiner respectfully disagrees with such an argument. Steenbergen is very clear about the existence and production of a specific polysialyltransferase in E.coli K92 that synthesizes a sialyl α2,8-2,9 polymer, identifies the same by Maxicell analysis of nested deletions coupled with *in vitro* transcription-translation assays. Therefore it is not clear to the Examiner as to what appellant means by "supported genetic evidence only" in the above argument and in what way such a teaching does not convey that a polysialyltransferase was characterized.

Next, appellant appears to make an issue of the purity of the enzyme isolated by Steenbergen et al. and argues that-

" Steenbergen stops short of actually disclosing that K92 sialyltransferase is, by itself, a polysialyltransferase capable of synthesizing a polysialyl α 2,9- α 2,9 linked polymer" and that "Steenbergen was unable to claim a disclosure that K92 sialyltransferase is a polysialyltransferase because Steenbergen failed to purify K92 sialyltransferase to homogeneity".

It is not clear to the Examiner as to why the purity of the enzyme is an issue to the appellant. This is because claims are not limited to a purified enzyme and therefore, whether the enzyme in the reference(s) was fully purified or partially purified or was a crude preparation is immaterial to the claim limitation. Claim 7 is simply drawn to a method of contacting the enzyme with its substrates. Therefore, appellant's argument about the purity of the enzyme is highly misplaced.

Appellant quotes from Vann reference in order to support his argument regarding the purity of the enzyme. Examiner respectfully asserts that the quotation from Vann reference does not in any way negate the teachings of Steenbergen et al. reference and in no way helps to argue against the rejection because this is a tangential argument which does not take into account the actual claim limitations.

With respect to the reference of Van Dijk appellant argues that the reference does not teach that alkaline phosphatase would be useful for releasing phosphate from CMP in connection with a synthetic process for producing a polysialic acid product having alternating α 2,8 - and α 2,9 linkages using a polysialyltransferase. In response Examiner would like to remind the appellant that the above rejection is an obviousness rejection and Examiner's argument is that it would have been obvious to those skilled in the art to apply the method of Van Dijk here to remove the CMP as opposed to a rejection under anticipation, wherein it is required that the reference disclose each claim element. Therefore, Examiner considers the above argument also as highly misplaced argument.

Finally, appellant argues that the present invention is enabled by the development and use of a modified polysialyltransferase as shown in Figure 2b of

the specification and that the "membrane protein" of the present invention is distinguished from the "membrane bound a2,9/a2,9 polysialyltransferase" by the addition of a hexomeric histidine at the amino end as in Figure 2b and that while the full length form of the protein a2,9/a2,9 polysialyltransferase of the present invention remains mostly in the membrane-bound form, 30-40% of the protein is released and this released protein retains full catalytic activity and is the kernel of the present invention. While that may be so, it can be clearly seen that claims are not drawn to said "kernel of the invention" and are drawn simply to the polysialyltransferase of *E.coli* K92. Appellant again goes through the tangential argument that the DNA plasmid disclosed in Steenbergen et al. does not encode the membrane protein of Figure 2b having a hexomeric histidine at the amino end and that there is no teaching by the Steenbergen reference that any fraction of the K92 sialyltransferase is released from the membrane fraction or that such released fraction would retain full catalytic activity. However, as stated above, all such arguments to overcome the above rejection are highly misplaced because claims are not drawn to a method of using either a modified enzyme or an enzyme that is partially released from the membrane. Appellant continues his argument that the present application teaches, for the first time, that α2,9/α2,9 polysialyltransferase is capable, without assistance from another membrane enzyme, of catalyzing a cell-free enzymatic synthesis of a polysialic acid product having alternating α2,9/α2,9 linkages of sialic acid and that contrary to the Examiner's allegation, the cited prior art does not disclose Step A of claim 7 etc. Again Examiner reiterates, that none of these arguments address the deficiency of claims or the present claim limitations which are much broader than what is argued by the appellant.

For all the above reasons, it is believed that the rejection should be sustained.

Respectfully submitted,

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Primary Examiner
Art Unit 1652

February 15, 2005

Conferees

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